

Editorial  
**Energizing Diastole**



Ragavendra R. Baliga, MD, MBA



James B. Young, MD

*Consulting Editors*

Epidemiologic studies suggest that diastolic dysfunction is present in more than half of the patients admitted to the hospital with congestive heart failure [1], and the mortality rate in these patients appears comparable to that of patients with depressed left ventricular ejection fraction. As there are few randomized clinical trials that include patients who have diastolic heart failure, current therapies have focused on the management of factors that exacerbate the clinical manifestations, such as lowering systolic and diastolic blood pressure, controlling ventricular rate in atrial fibrillation, and decreasing volume overload [2]. Unfortunately, the impact of available therapies on diastolic heart failure has been, at best, moderate, making the search for a more effective treatment urgent [3,4]. Recent work suggests that modulating myocardial energetics merit attention in this quest [5–7].

Intuitively, it is well recognized that sarcomeric relaxation is an active process because skeletal muscle goes into contracture (rigor mortis) rather than relaxation when metabolism stops. Abundant evidence exists that ventricular diastole is also an active process [8,9], because adenosine triphosphate (ATP) is required for the dissociation of actin and myosin in the cardiac myocyte [10–12]. Agents such as D-ribose that enhance

recovery of depressed myocardial ATP levels improve diastolic compliance [13,14]. “Running-out-of-gas,” or energy depletion, in the cardiac myocyte [10] was described in heart failure more than three decades ago [15,16], and several studies have characterized the impaired myocardial metabolism in diastolic dysfunction [17–22] and left ventricular hypertrophy (LVH), which often precedes diastolic dysfunction [23–28].

Myocardial energetics are complex [29], and currently the three best understood facets include energy substrate utilization, oxidative phosphorylation, and ATP transfer and utilization (Fig. 1). Substrate utilization, or the energy that is derived from ingested food, involves uptake of glucose and free fatty acids by the cardiac myocyte, the breakdown of these components by glycolysis and  $\beta$ -oxidation, and the entry of resulting metabolites into the Krebs cycle. The production of energy by the mitochondrial respiratory chain involves the production of high energy ATP molecules by phosphorylation of adenosine diphosphate (ADP) molecules and is known as *oxidative phosphorylation*; this process is the source of all energy reactions in the cardiac myocyte. The creatinine kinase energy shuttle is the process for ATP transfer and utilization [30]. Perturbation in each one of these three facets of

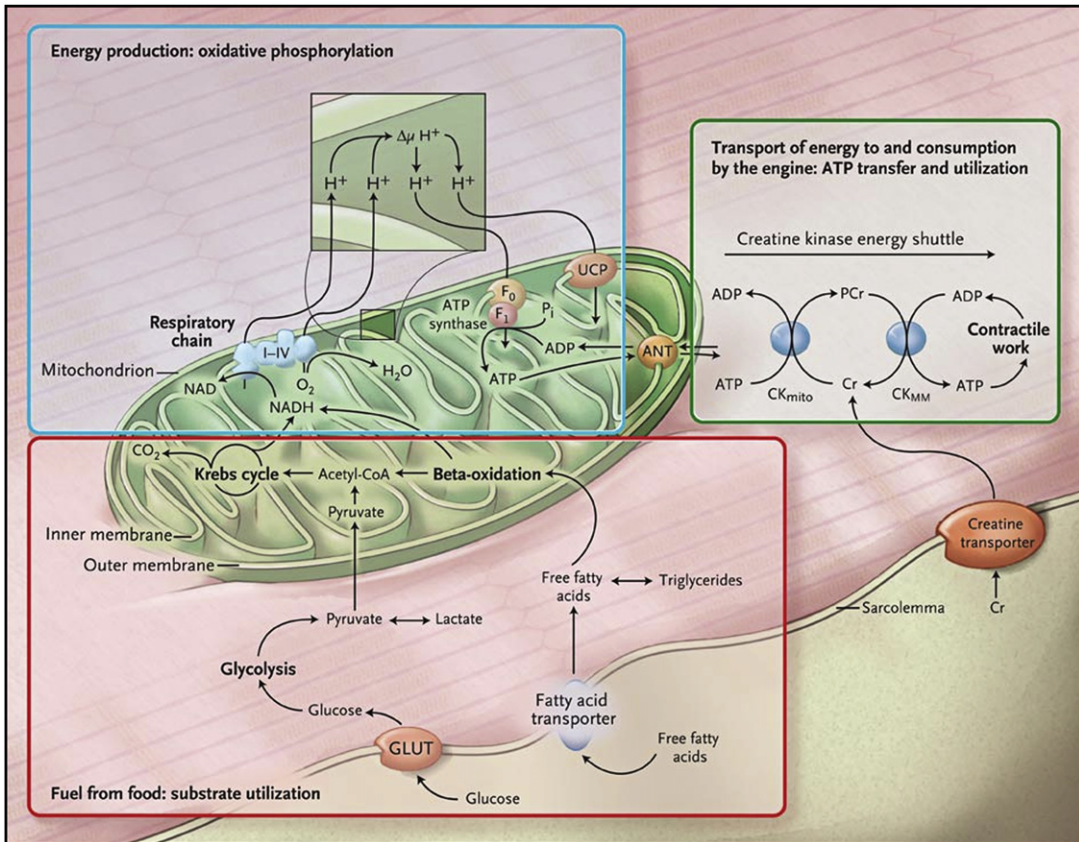


Fig. 1. Cardiac energy metabolism. Energy metabolism in the heart has three components. The first is substrate utilization (outlined in red), the cellular uptake of substrates and their breakdown by beta-oxidation and glycolysis; these processes result in the formation of acetyl coenzyme A (CoA), which is fed into the Krebs cycle and produces NADH and carbon dioxide (CO<sub>2</sub>). The second component is oxidative phosphorylation (outlined in blue), the production of energy. Respiratory-chain complexes I through IV transfer electrons from NADH to oxygen, thereby creating a proton electrochemical gradient ( $\Delta\mu H^+$ ) across the inner mitochondrial membrane as well as NAD and water. This gradient drives the F<sub>1</sub>, F<sub>0</sub> ATP synthase, which produces ATP by phosphorylating ADP. Uncoupling proteins (UCPs) cause mitochondria to produce heat rather than ATP. The third component is energy transfer and utilization (outlined in green), the transport of energy to and consumption by myofibrillar ATPase and other ATP-consuming reactions, such as sarcolemmal and sarcoplasmic reticulum ion pumps. ATP transfer is achieved by the creatine kinase energy shuttle. Creatine, which is not produced in the heart, is taken up by the creatine transporter. ANT, adenine nucleotide translocase; CK<sub>mito</sub>, mitochondrial creatine kinase isoenzyme; CK<sub>MM</sub>, myofibrillar creatine kinase isoenzyme; Cr, free creatine; GLUT, glucose transporter; PCr, phosphocreatine; P<sub>i</sub>, inorganic phosphate. (From Neubauer S. The failing heart—an engine out of fuel. *N Engl J Med* 2007;356(11):1140–51; with permission. Copyright © 2007, Massachusetts Medical Society.)

myocardial metabolism precedes or accompanies diastolic dysfunction. LVH is accompanied by change in distribution of the enzyme lactate dehydrogenase, which participates in glycolysis, and it is widely accepted that both glucose uptake and utilization increase in myocyte hypertrophy, although it is unclear how long this is sustained [10,20,21]. This increase in glucose utilization is

accompanied by a decrease in fatty acid oxidation in the hypertrophied heart. The increase in glycolytic rate or adenylate kinase reaction velocity occurs as a compensatory reaction to the decrease in creatine kinase reaction velocity caused by decreases in creatine and creatine kinase-isozyme activities [10]. All of these changes in the ATP synthesis pathways in the cardiac myocyte eventually

result in an inability to meet the chronic demands for ATP. Increased cytosolic ADP concentration occurs during diastolic heart failure as a result of a decrease in phosphocreatine concentrations (PCr) without a concomitant decrease in creatine. It has been hypothesized that these increases in the average cytosolic ADP concentrations in the absence of changes in any of the other known regulators of myofilament function result in sufficient slowing of cross-bridge cycling and thereby cause diastolic dysfunction (Fig. 2) [10, 31,32]. Successful modulation of diastolic heart failure, therefore, depends on the discovery of novel pharmacologic, genetic [22], or mechanical methods [33] that favorably modulate each one of three components of the metabolic machinery in the cardiac myocyte at any early stage. Some of these interventions include augmenting ATP or PCr stores, ATP synthesis, or  $\Delta G \sim \text{ATP}$  [2]; inhibiting carnitine palmitoyl transferase; and improving insulin sensitivity [34], substrate modification, or kinase modification [5,35]. D-ribose [14], perhexiline [36], ranolazine [37], and trimetazidine [38] are metabolic modulators that are currently under investigation for modulating cardiac myocyte metabolism [39].

Understanding the urgent need for developing effective therapies for diastolic dysfunction,

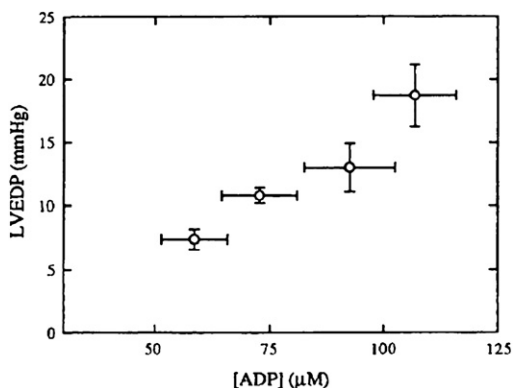


Fig. 2. Relationship between the increase in [ADP] and the increase in LV end-diastolic pressure (EDP) in isolated perfused rat hearts, in which [ADP] was altered by inhibiting creatine kinase to varying extents. Because all other known regulators of EDP were help-constant, these results show that increased [ADP] is sufficient to slow cross-bridge cycling in the heart. (From Tian R, Christie ME, Spindler M, et al. Role of MgADP in the development of diastolic dysfunction in the intact beating rat heart. *J Clin Invest* 1997;99(4):745–51; with permission.)

Mani Vannan, MD, and Bertram Pitt, MD, have put together a stellar panel of contributors whose articles should provoke further research in diastolic heart failure. These authors have focused on important cutting edge aspects of diastolic dysfunction. In this editorial, we have focused on myocardial metabolism as this concept has been in the forefront more recently [5–7,29,35]. In our opinion, modulating myocardial energetics [36–39] could emerge as an important strategy to improve outcomes in diastolic heart failure [6,7,30]; the future could very well be in “revving-up” diastole. Energizing diastole, or specifically myocyte metabolism, may not only be effective therapy for diastolic heart failure but also someday may be the standard of care for the prevention and treatment of all clinical forms of heart failure.

Ragavendra R. Baliga, MD, MBA  
The Ohio State University  
Columbus, OH, USA

E-mail address: [Ragavendra.Baliga@osumc.edu](mailto:Ragavendra.Baliga@osumc.edu)

James B. Young, MD  
Lerner College of Medicine  
Cleveland Clinic  
Cleveland, OH, USA

E-mail address: [YOUNGJ@ccf.org](mailto:YOUNGJ@ccf.org)

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